REMARKS

Entry of the foregoing and favorable reconsideration of the subject matter application, as amended, pursuant to and consistent with 37 CFR §112, and in light of the remarks that follow are respectfully requested.

With a view to overcoming the Examiner's objections, an amended set of claims is filed with the present response. Specifically, claims 1, 11, 13, 16, 17, 24 and 30 have been amended. Claims 10, 20, 21 and 29 have been cancelled without prejudice.

Support for the claim amendments presented herein can be found throughout the specification and in the claims as filed. The claim amendments will be further discussed in connection with the issues discussed herein.

ELECTION/RESTRICTIONS

The Examiner made his election/restriction requirement final, despite the arguments submitted by Applicant.

Group I is therefore elected and claims 3-10, 12, 22, 25-28 and 31 stand withdrawn as being directed to non-elected invention(s). However, the Applicant reserves the right to prosecute the non-elected subject matter, as well as the originally filed claims, in one or more divisional applications.

PRIORITY

The Examiner has requested Applicants to submit a certified copy of the prior French application FR9908502 as required under 35 U.S.C. § 119(b). Applicant respectfully submits that it has fully complied with all rules for perfecting priority.

According to P.C.T. Rule 17.2(a) (2003), a designated Office may request that the International Bureau send it a certified copy of an earlier national or international application ("the priority document") from which priority for a national stage application is claimed. Under Rule 17.2(a), the priority document shall be submitted to a designated Office by

the International Bureau, not the applicant, if (1) the applicant has complied with Rule 17.1(a) or (b), and (2) the international application has been published. Rule 17.2(a) further provides that "[n]o [designated] Office shall ask the applicant himself to furnish it with a copy."

An applicant has complied with Rule 17.1(a) if a certified copy of the priority document was "submitted by the applicant to the International Bureau or to the receiving Office not later than 16 months after the priority date".

An applicant has complied with Rule 17.1(b) if the applicant requested that the same receiving Office that issued the priority document "prepare and transmit the priority document to the International Bureau" within "16 months after the priority date".

In this case, Applicant has complied with the relevant rules by submitting the French priority application FR 9908502 to the required authority, and the corresponding international application has been published. Thus, Applicant has complied with the requirements of Rule 17.2(a), and should not be required to submit another certified copy of the priority document to the designated Office.

REJECTIONS UNDER 35 U.S.C § 112

Claim 1 has been rejected as being vague and indefinite in terms of whether diagnosis or monitoring is being performed. As pointed out by the Examiner, diagnosing and monitoring the evolution of a synovial disease are two different activities as the ultimate step of the diagnosis involves theoretically a "yes" or "no" response, whereas the ultimate step of the monitoring involves the determination of a progression.

However, Applicant submits that the method of claim 1 is clear and definite in that covers both diagnosis and monitoring, as indicated, for example, by the fact that these recitations are described in the alternative. Plainly, the possible

outcomes of a comparison between the determined level of the specific marker with a reference level will include a determination that the determined value is higher than the reference or that the value is lower than the reference. In the case of a diagnosis, for example, the chosen reference level might be the mean level of a sample of healthy persons. In this situation, a determination that the value is higher than the reference would prompt a diagnosis of synovial disease, whereas a value that is about the same or lower than the reference would not result in such a diagnosis.

In the case of monitoring the progression of a synovial disease, the chosen reference level might be for example, the level of the specific marker that was previously determined. In this situation, if the determined value is higher than the reference, one skilled in the art would understand this to mean that the synovial disease has progressed. On the other hand, and if the value is lower than or unchanged from the reference, one skilled in the art would likely take this to mean that the synovial disease has not increased.

Therefore, depending on the chosen reference, the result of the comparison allows a diagnosis or the monitoring of the evolution of a synovial disease.

In conclusion, it is thus clear that the method of claim 1 is clear and definite with respect to diagnosis and monitoring of the evolution of a synovial disease.

Claim 1 has also been rejected as being vague and indefinite as to the specific marker.

Claim 1 has been amended to recite that glycosylated pyridinoline is the specific marker for synovial disease, support for which is set forth on page 2 of the present application. Accordingly, claim 10 has been cancelled and claim 11 has been made dependent on claim 1.

The same amendment has been made to claim 24 directed to a kit, which now recites that the specific marker for synovial disease is glycosylated pyridinoline. Accordingly, claim 29 has been cancelled and the dependency of claim 20 has been amended.

To overcome the objection to claim 1 (paragraph iii), the recitation "optionally" has been deleted.

In view of the foregoing, Applicant respectfully requests that the Examiner withdraw each ground of objection to claim 1.

Claim 2 has been rejected as vague and indefinite with respect to what Applicant is trying to cover, and that the claims appear to cover all individuals having synovial disease and those susceptible of developing synovial disease. In response, Applicant has amended claim 2 to recite "monitoring". The recitations pertaining to diagnosis have been deleted. They are now presented in claim 32, additional support for which is set forth on page 8, paragraph [0044] of the English specification.

In view of the foregoing, Applicant respectfully requests that the Examiner withdraw the objection to claim 2.

Claim 13 has been rejected on the ground of lack of proper antecedent basis for the recitation "the destructive or non destructive stage". In response, the term "the" has been changed to "a".

Claim 16 has been rejected as being vague and indefinite on the ground that it is unclear whether Applicant intends to use the acronym (HPLC) in an art-recognized fashion. In response, this claim has been amended to further define the acronym in accordance with art-recognized usage, namely "High Performance Liquid Chromatography."

Claim 17 has been rejected as being vague and indefinite on two grounds, namely whether the parenthetical recitations are part of the claim, and the nature of the functional relationship between creatinin and the specific marker.

In response, this claim has been amended to delete the parenthesis. Aside from that, Applicant submits that creatinin is a well-known standard reference. In fact, urinary samples can exhibit a very large range of concentrations of solutes. With a view to determining the level of a marker in such sample, it is therefore desirable to normalize the detected value, with an index for expressing concentration of urinary sample. This is commonly done by reference to the concentration of creatinin. An illustration of this use of creatinine is described in prior art of record. Specifically, Sinigaglia, *et al.*, cited in the International Search Report and IDS, points out that the concentrations of Hydroxypyridinoline (HP) et Lysylpyridinoline (LP) "are expressed as pmol/µmol of creatinine in urinary samples..." (which is equivalent to nmol/mmol of creatinin) (see page 145, lines 20-21 of the left column). On the basis of this evidence, Applicant submits that one skilled in the art would have understood the significance of the reference to creatinine, within the context of the invention of claim 17.

Claim 20 has been cancelled without prejudice, rendering the objections to this claim moot.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of each and every ground of rejection under 35 U.S.C. § 112, second paragraph.

REJECTIONS UNDER 35 U.S.C. § 102

Claims 1, 2, 16, 18 and 19 have been rejected under 35 U.S.C. § 102(b) as being unpatentable over Blum, *et al.*, Eur. J. Clin. Invest. *25*:438-441 (1995) ("*Blum*"). Applicant respectfully submits that *Blum* does not disclose the presently claimed invention. Specifically, there is no disclosure in *Blum* of measuring glycosylated pyridinoline to diagnose or monitor progression of a synovial disease. Being that pyridinoline may be non-glycosylated, glycosylated or di-glycosylated (see paragraph 13 of the present specification), it cannot be even be

said that *Blum* would have "inherently" anticipated the claims. Accordingly, reconsideration and withdrawal of the present invention are respectfully requested.

Claims 1, 2, 14, 15, 18 and 19 have been rejected under 35 U.S.C. § 102(b) as being unpatentable over Price, *et al.* (W095/02188) ("*Price*"). Applicants respectfully submit that *Price* does not disclose the presently claimed invention.

Price discloses the use of the protein YKL-40 as a marker for degradation of mammalian connective tissue matrices, and specifically that the serum level of YKL—40 can be correlated in a mammal to the presence and status of diseases in which matrix metabolism plays a role (see for example page 1, lines 12-15). There is no disclosure in *Price* of measuring glycosylated pyridinoline to diagnose or monitor progression of a synovial disease. Accordingly, reconsideration and withdrawal of the present invention are respectfully requested.

REJECTIONS under 35 U.S.C. § 103

Claims 10, 11, 13, 20 and 21 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Blum* in view of Robins, *et al.* (W089/12824) ("*Robins*"). The Examiner has determined that it would have been obvious to one of ordinary skill in the art to incorporate glycosylated pyridinoline and diglycosylated pyridinoline as the markers for the method of *Blum* because *Robins* shows that glycosylated pyridinoline and diglycosylated pyridinoline are markers that are specific to a particular tissue of origin. Applicant respectfully disagrees that the collective teachings of the cited prior art establish a case of *prima facie* obviousness.

First, claims 20 and 21 have been cancelled. Aside from that, *Blum* does not teach a method of diagnosing or monitoring progression of a synovial disease by measuring levels of glycosylated pyridinoline or diglycosylated pyridinoline. *Blum* is totally silent with respect to these molecules - this

publication is directed to measuring "pyridinoline" and using "purified pyridinoline" as a standard. In addition, *Blum* (page 438, right column) states that "pyridinium cross-links of collagen, pyridinoline (Pyr) and deoxypyridinoline (D-Pyr), are issued from the degradation of mature collagens of bone and cartilage." This statement is not indicative of, and thus would not have been suggestive of synovial collagen degradation.

Robins does not remedy the deficiencies of *Blum*. *Robins* discloses the measurement of glycosylated lysyl or hydroxylysyl pyridinoline in the context of bone disorders and arthritic diseases. More specifically, *Robins* mention that measurement of these glycosylated pyridinoline derivatives is indicative of bone collagen resorption and that measurement of diglycosylated pyridinoline is indicative of bone or cartilage degradation (see W089/12824 page 6, lines 13-16). See also page 3, which teaches that the collagen may suitably be associated with bone or cartilage. There is no disclosure in *Robins* of the use of glycosylated or di-glycosylated pyridinoline as markers specific for synovial disease. There is no mention or suggestion of synovial collagen degradation.

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 20, 24 and 29 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Blum* in view of *Robins* as applied to claims 1, 2, 10, 11, 13-16 and 18-21, and further in view of Boguslaski, *et al.* ("*Boguslaski*"). The Examiner has determined that the teachings of *Blum* and *Robins*, taken together, differ from the present application simply in terms of failing to teach packaging the components into a kit, and that this deficiency is supplied by the teachings of *Boguslaski*. Applicant respectfully disagrees that the collective teachings of the cited prior art establish a case of *prima facie* obviousness.

First, claim 20 has been cancelled. With respect to claims 24 and 29, Applicant's arguments with respect to *Blum* and *Robins* are repeated herein as they apply equally. The teachings of *Boguslaski*, therefore, simply do not come close to the mark. There is no disclosure or suggestion in this publication regarding such a marker.

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: December 8, 2003

Respectfully submitted,

By Shawn P. Foley

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